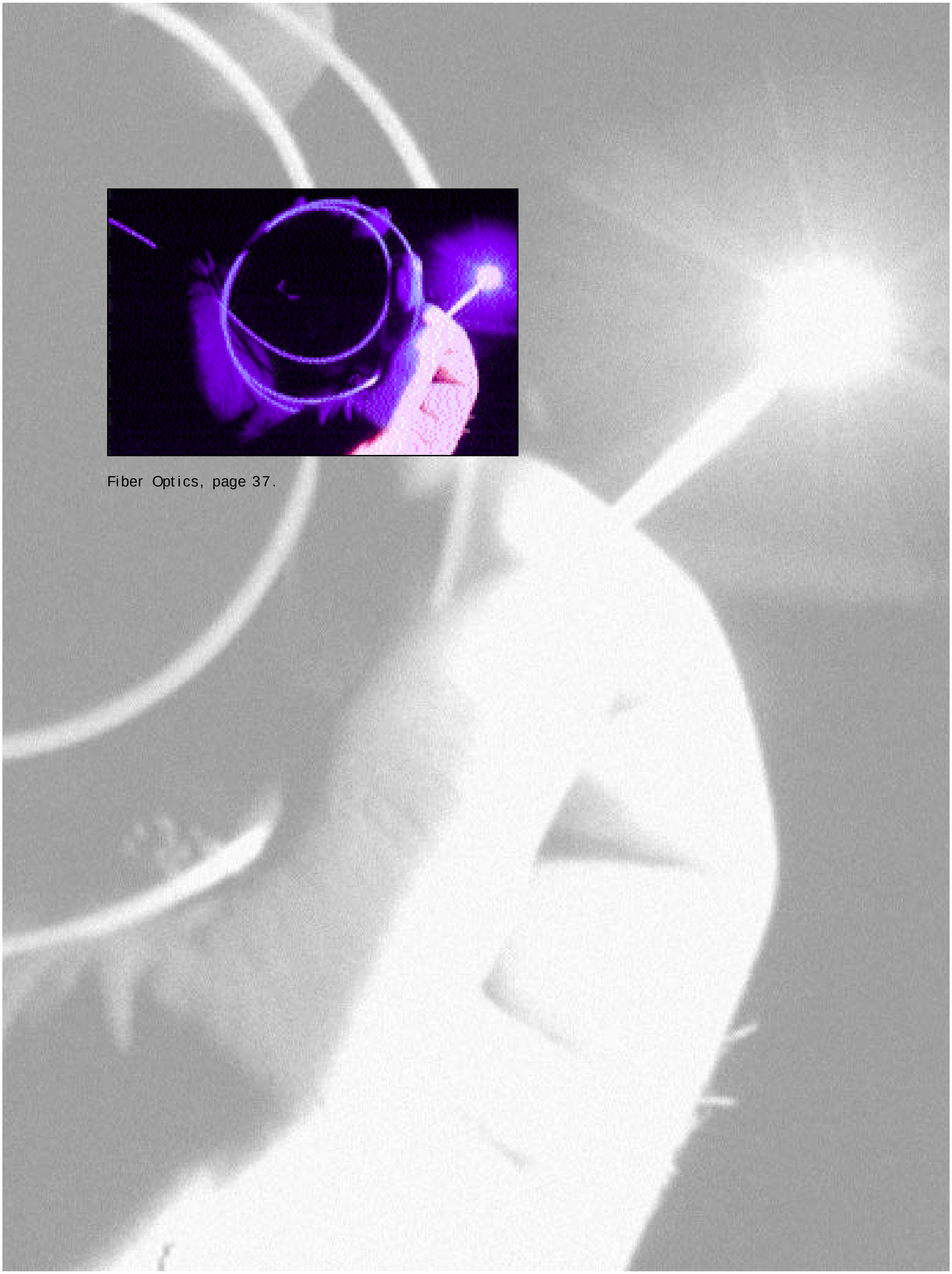


Fiber Optics, page 37.

Existing Technologies

Many well-established medical technologies can benefit from refinement in materials and methods. In medical radiography, for example, resolution of images depends heavily both on how X-rays are scattered in tissue and on technician skill. Film storage leads to scratching and degradation of important baseline imagery. Real-time acquisition of images for patient comfort and for use in surgical guidance are also key factors in controlling radiation exposure and medical costs. Magnetic resonance imaging, a data-intensive image-gathering technique, can benefit from faster data upload and download, higher magnetic field strength, and lower cost. Work continues in the application and fine-tuning of medical lasers. Directed beam therapies and radiopharmaceuticals are fairly recent additions to the proven clinical arsenal and are a rich ground for innovation.Many BMDO-supported technologies can contribute to their impact on health care.

X-Rays

In 1895, a physics professor named Wilhelm Roentgen was experimenting with cathode ray tubes. After one of these experiments, he noted that phosphor screens near the tube were glowing and eventually concluded that the cathode ray tube was responsible. The invisible source of excitation was given the name X-ray, after that favorite term for an unknown, "x." This observation that X-rays could penetrate containers led to the most common of imaging diagnostic procedures.

One hundred years later, one of the biggest improvements in X-ray technology has been the development of computerized axial tomography (CAT). In 1970, X-ray imaging was combined with computer power to create clear, cross-sectional views of an object. The technique was so significant that it won a Nobel prize in physiology for inventors Godfrey N. Hounsfield and Allan M. Cormack of Tufts University. In CAT scans, an X-ray scanner is rapidly rotated around the subject, yielding high-resolution images of the body's interior that often provide more information than conventional two-dimensional X-ray images. In spiral or helical scanning tomography, a recent innovation in this area, X-ray delivery occurs in a rotating spiral pattern, as opposed to the slice-by-slice, conventional CAT scan pattern. Digital image enhancement can be combined with CAT imagery to improve contrast and sharpen detail.

Strengths

Because of its ubiquitous use in rapid imaging of medical problems from broken bones to ulcers, X-ray imaging has become highly available and relatively inexpensive. X-rays have been quantitatively assessed for dosage limits. Angiography and angioplasty require use of X-rays,as do gastrointestinal series, spinal studies, and detection of primary and metastatic cancers. Chest X-rays can be used to confirm diagnoses as diverse as pneumonia, tuberculosis, chronic asbestos exposure, or an enlarged heart. X-ray-based mammography is generally accepted as a screening method for early breast cancer detection.

Limitations

Since X-rays are a source of ionizing radiation and are therefore potentially mutagenic, their use is limited by recommendations for yearly or lifetime exposure. In addition to being a reader-dependent diagnostic art, it is a technique-dependent method. The film images produced by X-ray are gray-scale and could benefit greatly from resolution enhancement techniques or by eliminating film and converting radiation to digital storage (e.g., through a charge-coupled device). Image quality is also partially dependent upon the radiation's penetration of and scatter throughout the tissue, and these phenomena can differ widely, depending on body type, fat percentage, and so on.

Although mammography is an entrenched screening tool for breast cancer, it is still subject to the outcome of various longitudinal studies and debate. There is a consensus that mammography is a reasonable trade-off between radiation exposure and tumor detection for women over 50. For women younger than 50, opinions vary widely because the dense breast tissue characteristic of premenopausal women is difficult to image with mammography. Advances in image enhancement and computer-aided diagnosis can provide answers to help resolve this continuing debate. Current mammography enables detection of abnormalities as small as 5 mm in diameter, as well as submillimeter calcifications that can be indicative of cancer. Except in highly macroscopic conditions, the radiologist looks for changes in successive mammograms, ideally with a baseline image as an initial point of reference.

Digital Mammography Eliminates Film

BMDO Technology Background

BMDO research in industrial radiography led directly to a new method of digitizing images for mammography, including computer-aided diagnostic techniques. As in numerous other labs and companies, the effort is to make mammography a “filmless” experience. This work is supported by a cooperative research and development agreement (CRADA) between Lawrence Livermore National Laboratory (LLNL; Livermore, CA) and Fischer Imaging (Denver, CO).

How It Works

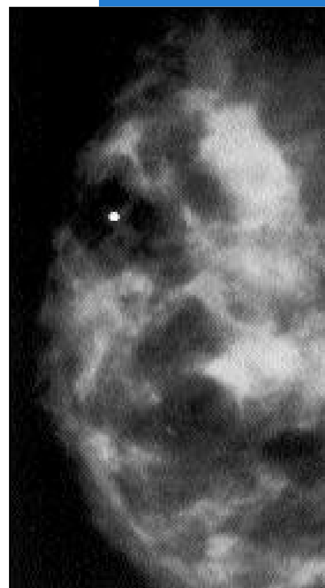
In filmless mammography, the X-rays pass through the breast and into a scintillating material, where they are converted to visible light. The light travels through a fiber-optic reducer, which is a bundle of individual fibers that is stretched so that one end is larger in cross-sectional area than the other. For example, this allows a 2 cm x 2 cm area of breast image to be captured on a 1 cm x 1 cm charge-coupled device (CCD). It currently takes an array of about 20 CCDs to record a full breast image. Fischer’s device takes about 4 seconds to acquire an image.

Potential Use to Medicine

Researchers hope to build a system that will identify all of cancer’s warning signs, making computer-aided diagnosis a viable commercial option. A dental apparatus to screen images of teeth for signs of decay is also a possibility. Researchers at LLNL are working on programs to recognize and flag danger signs in digital mammograms so that cancer can be detected and treated even at its earliest stages. In particular, they are developing an algorithm by which the computer will spot microcalcifications, which appear as tiny specks scattered across the image and are often missed by the human eye. The same program will then flag possible trouble spots for further scrutiny by radiologists.

Product Status and Availability

Under a CRADA signed by LLNL and Fischer Imaging in October 1993 a complete digital mammography system will be designed from the floor up, including the means to capture images electronically and send them directly to the computer. A working prototype is expected by 1996.



Credit: Mitchell D. Schnall, M.D., University of Pennsylvania

▲ White dot on mammogram indicates palpable abnormality.

Fiber optics and new image acquisition materials can make mammography a filmless experience.

New Technique Peers Into Bones and Teeth

Conventional X-ray of rheumatoid arthritic swelling in a hand. ▲

Pharmaceutical firms, such as Eli-Lilly, Procter and Gamble, and Merck, are interested in using XTM in their drug research.

BMDO Technology Background

A new and powerful X-ray technique developed at Lawrence Livermore National Laboratory (LLNL; Livermore, CA) and Germany's University of Dortmund allows researchers a three-dimensional look at the interior of materials such as industrial ceramics, metal matrices, bones, and teeth. BMDO-sponsored research at LLNL and Sandia National Laboratories led to the development of this technique, called X-ray tomographic microscopy (XTM). XTM is similar to CAT scanning and has a resolution of about 1 micron, which is roughly 500 to 1,000 times sharper than CAT.

How It Works

In the XTM apparatus, X-ray photons pass through a sample positioned on a rotating stage. They are then converted to visible light on a scintillator screen and imaged with a two-dimensional CCD detector. The CCD allows multiple, contiguous tomographic cross sections to be collected at the same time, so the volume can be viewed in cross section by slicing through the structure in any planar direction. Such planes can be combined to produce a three-dimensional rendering of the structure, emphasizing material of either higher or lower density. A strain microscope attachment developed by Sandia allows examination of structures under load.

XTM can use either synchrotron-produced or conventional X-ray sources but a synchrotron radiation source results in the highest resolution. XTM can obtain 2,000 image "slices" in less than an hour.

Potential Use to Medicine

XTM is currently being used to study the microstructure of bones and teeth. With a grant from the National Institutes of Health (NIH) and the National Institute of Dental Research, researchers are using XTM to map mineral distribution in teeth. This research can shed light on how dental caries (cavities) form and may lead to improved filling composites.

XTM can also image the lacy, inner matrix of bone and reveal how bone loss and bone formation occur. An understanding of these processes can help researchers devise new remedies for osteoporosis and arthritic bone degradation, and perhaps help to explain how estrogen retards bone loss.

Researchers are also looking at the utility of XTM in catheterization procedures such as balloon angioplasty. The main obstacle to this use is the large size of synchrotrons needed as an X-ray source.

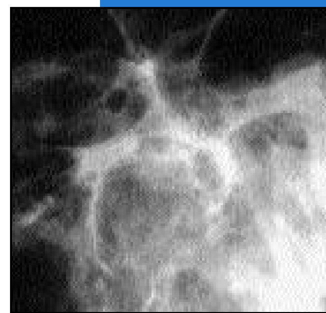
Product Status and Availability

In vivo studies in bone loss are now being conducted with XTM at the University of California, under a 3-year NIH grant. Drug companies such as Roche Bioscience are actively working with LLNL, using XTM to determine how steroidal drugs break down bone. Other pharmaceutical firms, such as Eli-Lilly, Procter and Gamble, and Merck, are also interested in using XTM in their drug research. Dr. John Kinney, principal investigator at LLNL, is interested in collaborative research proposals from other companies, as well.

From Infrared to X-Ray

BMDO Technology Background

NOVA R & D (Riverside, CA) is working on a scanning digital mammography unit with higher spatial resolution, lower radiation, and better display with higher contrast than present mammography methods. The key to the system is a silicon pixel detector (SiPD) developed for BMDO systems at Hughes Aircraft Company (El Segundo, CA). Hughes developed SiPD technology for use in infrared sensors. NOVA proposed a modification of these silicon pixel devices for X-ray detection in digital mammography. The X-ray detector was an adaptation of the infrared sensor technology.



Credit: Dr. Martin Yaffe

▲ An image obtained with a CCD-based scanning digital mammography system.

How It Works

SiPD places thousands of individual detector pixels in a single semiconductor substrate, which is connected to a front-end readout electronics chip with a time-delayed integration-charge-coupled device (TDI-CCD) function. The sections have matching pixel geometry and are electrically connected through an indium bump bonding technique, which allows each diode to be directly connected to its readout electronics. This setup in turn enables the fabrication of small-capacitance and low-noise detectors. NOVA's systems could also be used for bone densitometry and panoramic dental X-rays.

Potential Use to Medicine

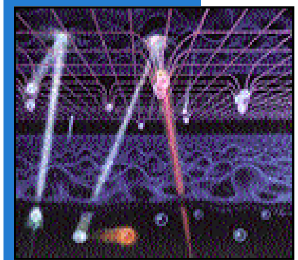
Dr. Martin Yaffe of the Sunnybrook Health Science Centre in Toronto has been collaborating with NOVA. Dr. Yaffe's research in digital mammography has helped NOVA in its quest to reduce radiation dosage, eliminate the need for a grid (used in conventional systems to reduce scatter), improve image resolution, and produce a filmless X-ray that can be electronically stored and transmitted. Dr. Yaffe is currently using a scanned slot system with a detector array that is 50 to 500 x 5,000 to 6,000 pixels. The detector is moved in one direction as X-rays are delivered to the breast, capturing incident radiation one section at a time; it takes 1 to 5 seconds to complete the scan. The sections are overlapped to create an image of the whole breast.

Silicon pixel technology will offer high-resolution, low-dosage mammography.

Product Status and Availability

NOVA plans to have a prototype silicon-pixel based mammography unit by 1997.

Novel Materials Aid in Mammography Design



Quantex Corporation's ET®s can help increase sensitivity of mammographic images.

Light-trapping materials can serve in computing, recognition, and visualization tasks.

BMDO Technology Background

In part through a BMDO phase 1 SBIR contract, Quantex (Rockville, MD) developed light-trapping materials for use in high-speed optical computers. Military areas impacted by this technology are missile identification, high data transfer rates, and massive optical storage capacity. Quantex named these materials ET®s for their electron-trapping ability.

How It Works

ET® storage media are composed of alkaline-earth chalcogenides doped with two or three rare earth elements. Visible and non-visible light (sunlight, fluorescent light, X-rays, etc.) energizes the ET® by raising the energy levels of electrons in the first dopant. These electrons decay into the ground state of a second dopant material, where they are "trapped." They can be held in this stable state for periods of several years or more. When exposed to infrared (IR) light, however, the trapped electrons again are raised to a higher energy state and then decay back to the ground state of the first dopant. As they decay to the original ground state, the electrons give off light (photons) in the visible spectrum. The emitted photons have an intensity that corresponds to that of the initial incident photons. For this reason, ET®s are excellent alternatives to conventional X-ray film; Quantex has created compounds that store X-ray images, which are also released when acted upon by incident IR light.

Potential Use to Medicine

Light-trapping materials lend themselves to the capture of incident radiation, for visible light as well as for X-rays. Quantex's material innovation is useful in many types of optical and imaging applications and has excellent potential to improve X-ray capture and to eliminate the "noisy" step of film processing. They can also retain trapped electrons for long periods, which translates to long-term data storage. ET®s are also intrinsically compatible with digital imaging and storage methods, which is important because digital images can be electronically transmitted and stored in areas remote to the image-acquisition site.

Quantex is making a substantial effort to improve the state of the art in mammography. By leveraging the company's ET®s into a solid-state mammography unit, the company plans to build a system that increases contrast sensitivity tenfold, eliminates film processing, and incorporates computer-enhancement of images. These improvements can lead to earlier detection of breast cancer, reduced radiation exposure for patients, and a standardized method for image capture. Images acquired in this fashion can also be transmitted to remote areas over standard communication lines, furthering telemedicine capabilities.

Product Status and Availability

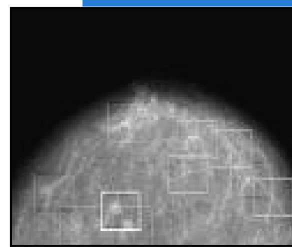
Quantex has received other SBIR awards for a filmless, digital, dental X-ray imaging system; a filmless mammography system promising superior resolution, dynamic range, and cost efficiency; and a new radiographic imaging system for protein crystallography analysis. The company has licensed a life-sciences company for radio- and chemiluminescent-tracer DNA imaging. Quantex has also licensed technology to another company engaged in nondestructive evaluation of nuclear power plants and the gamma/X-ray imaging field.

Defense Technology Targets Medical Imagery

BMDO Technology Background

In April 1995, Rose Health Enterprises (Denver, CO) and Lockheed Martin (Denver, CO) formed a company called MedDetect, LLC, to convert defense technology to medical image analysis applications. Lockheed Martin has had several contracts with BMDO to develop target recognition and acquisition technology; target scene generation software and optical components for rapid data processing are among these technologies. According to E. Michael Henry of Lockheed Martin, the target acquisition methods used for both military and medical applications are state of the art.

MedDetect's initial work is focused on optical processor capabilities in mammography. Fast optical computing of complex algorithms, as well as automated electronic analysis of mammogram images, are expected to make screening methods faster and more accurate.



▲ Bold white square indicates "region of interest," or possible abnormality, on this mammogram.

How It Works

The techniques used by MedDetect are a hybrid of optical and digital processing. An optical correlator uses a low-power laser and lenses to examine the mammographic image. The optical correlator uses photons instead of electrons to perform the calculations necessary to detect an abnormal feature. This information is then transmitted to a computer that uses neural network software to learn the specific attributes of breast abnormalities. The "learned" information is stored and applied to new images. This technology has been successfully demonstrated on military helicopters for identification of camouflaged ground vehicles.

Potential Use to Medicine

Approximately 90 percent of screening mammograms are negative; if some of these negative images can be assessed quickly, the physician can use the time saved to carefully examine and evaluate the remaining images. In addition, pattern recognition makes screening a more powerful tool by automatically tagging abnormal image attributes. In preliminary tests based on historical mammographic images, the technology has already identified a cancerous breast lesion that was not apparent for another year by conventional methods.

Optical processing can speed up image acquisition for mammography.

Mammography was estimated to have accounted for $1 billion in health care costs in 1994. MedDetect aims to reduce mortality through earlier detection, and to reduce mammography costs by speeding analysis and diagnosis.

This system will also be perfectly compatible with filmless digital mammography that is under development in companies such as Fischer Imaging (Denver, CO), NOVA R & D (Riverside, CA), and ThermoTrex (San Diego, CA). The X-ray image can undergo lesion analysis in less than a minute, transmitted to another radiologist for a second opinion, and then digitally stored in a centralized location. The latter capability is also important for baseline analysis of, quick access to, and comparison of images.

Product Status and Availability

Both Rose and Lockheed Martin are providing seed money for MedDetect and plan to raise additional private capital. A prototype should be available within 18 to 24 months. MedDetect also expects to use these optical processing methods to improve cancer detection in chest X-rays, Pap smears, and other cytological analyses.

Digital Imagery Outperforms Conventional X-Ray

Conventional mammogram compared to digital image.

BMDO Technology Background

Using advanced imaging techniques and digital technology originally developed for the Strategic Defense Initiative, ThermoTrex Corporation (San Diego, CA) has made a major contribution to the development of digital mammography. Through its LORAD division, ThermoTrex has built a prototype device that outperforms conventional mammographic imagery by expanding the nuances of gray-scale and by better detecting microcalcifications that can signal the presence of cancer. In November 1993, LORAD demonstrated the first full breast digital imaging system, which showed superior image acquisition, especially for the dense breast tissue of young women, for whom conventional mammograms are hard to read. In addition, LORAD uses this same digital technology in StereoGuide™, a stereotactic device, for positioning the breast for fine-needle biopsies and aspirations. This device provides accurate and minimally invasive investigation of breast tissue, and is being marketed successfully in the United States.

How It Works

Instead of using hard-to-store and scratch-prone X-ray film, ThermoTrex's prototype records X-rays in digital form using a charge-coupled device (CCD). In near-real time, an image of the breast is collected by the CCD, can be digitally enhanced if desired, and stored electronically. The image can be displayed on a computer monitor or printed on conventional film and also can be relayed to remote sites for consultation between radiologists. The digital format of the information means that computer-aided diagnostic algorithms can be used to analyze the mammogram.

For its stereotactic device, LORAD employs a 25 cm^2 field-of-view X-ray receptor, which can be used to view small areas of the breast targeted for fine-needle biopsy. By contrast, the full breast imager records a 6.75 cm x 6.75 cm section of the breast. The camera sequentially images 12 overlapping sections of the breast, and the resulting data is "stitched" to yield a seamless picture of the full breast. These electronic stitching methods were developed by the National Aeronautic and Space Administration for the Voyager spacecraft. The final image is in the form of a 3,072 x 4,096 pixel matrix, or 24 megabytes of data.

Superior images for accurate diagnoses and surgical guidance.

Potential Use to Medicine

The use of digital methods in mammography makes possible electronic transmittal and storage of X-ray images, direct application of computer-aided diagnostic algorithms, sharper and more accurate images for better lesion detection, and reduced exposure to radiation, all of which translate to early cancer detection, reduced risk, and improved survival.

Product Status and Availability

The digital mammography unit is still under development. A prototype device is installed at the University of California at San Diego's Center for Women's Health, where it has imaged 25 volunteers during 1995. Second-generation prototypes being installed at the University of Virginia (Charlottesville, VA) and at the University of California at Los Angeles will be used to collect patient data for Food and Drug Administration approval requirements. Images from the unit were showcased at the December 1994 meeting of the Radiological Society of North America and were favorably received by physicians from some of the country's premier oncology centers.

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Magnetic Resonance Imaging and Related Technologies

Nuclear magnetic resonance, or NMR, was first applied to medicine in 1977 by Dr. Raymond Damadian of the State University of New York's Downstate Medical Center (Brooklyn,NY). NMR uses a superconducting magnet to align the spin states of hydrogen atoms in cells of the body. When the magnet is turned off and the atoms "relax" to their normal alignment, they emit measurable frequencies. These frequencies are computed, using powerful algorithms, and an image is generated from the results. Protons that are tightly bound within molecules, such as those in bone, emit weak signals, while protons in aqueous environments emit strong ones. Magnetic resonance imaging (MRI) is a direct descendant of NMR.

Strengths

Because MRI produces no ionizing radiation, the entire body can be safely viewed without concern for exposure time. MRI can be augmented with injectable paramagnetic contrast agents such as gadolinium. This method is very useful in brain imaging, and to a lesser extent, in spinal studies. A recently developed investigative method for lung imaging with MRI involves the use of an inhaled gas. MRI has some value in assessing cancer, especially in investigations of disease recurrence, but it is not yet regarded as a reliable screening tool. It is especially good for imaging soft tissues and shows promise for blood flow studies.

Limitations

Despite its promise of accurate, noninvasive imaging, MRI is underutilized. The equipment is very expensive (about $1.5 million per unit cost) and patient throughput is slow. These costs, which are tied to throughput and materials, could be ameliorated with smaller equipment and high-temperature superconductors (i.e., more powerful magnets of smaller size). Patients with cardiac pacemakers and implanted metallic prostheses can't be imaged with this technique. Another limitation is that the tube in which the patient is placed often elicits feelings of claustrophobia, which has turned out to be a surprisingly significant problem. Children usually have to be sedated for MRI. Open magnet units are becoming increasingly available, but at the expense of magnetic field strength, according to one researcher.

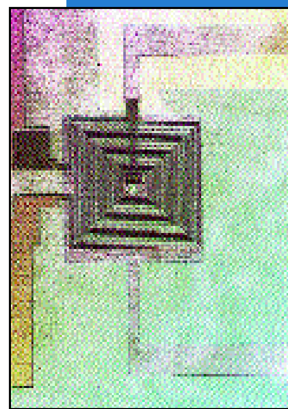
MRI, along with X-rays, computerized axial tomography (CAT), and ultrasound, represents a complement in the field of imaging. It images some anatomical features very well, but fails, for instance, in visualization of bone. It is an important method for visualizing tumors in parenchymal tissue, such as the liver. A 0.4 T field MRI machine requires up to an hour to create a good image. While MRI is promising for diagnosis of breast, prostate, and other cancers, its capacity to examine stages of known cancers must be evaluated further before it can be used for detection. Some studies in prostate carcinoma find that MRI misses up to 40 percent of cancers, and has a lower limit of detection of 5 mm.

Cost is an important issue in this era of declining resources and the limits of third-party payers.Reducing the size, but not the strength, of the magnet, and increasing the speed of throughput, would lower the prices of the scans. Helium-based superconductors are expensive, and helium itself boils away rapidly. Hence,high-temperature superconductors would be useful in driving down costs as well. Data upload and download are also time-consuming and inefficient, and comprise a good deal of the preparatory stages for MRI. Hence, software design and the use of parallel processors are valuable to this technology.

High-Temperature Superconductors Instrumental for MRI

BMDO Technology Background

Conductus (Sunnyvale, CA) has performed a variety of BMDO-related research projects on high-temperature superconducting (HTS) materials. As a well-established manufacturer of magnetic sensing instrumentation, the company has been able to apply its innovations to components for NMR equipment, MRI, and magnetic sensing of the heart.



▲ A high-temperature SQUID magnetometer.

How It Works

MRI applications. Conductus uses a proprietary thin-film technology to process HTS products based on yttrium barium copper oxide (YBCO). YBCO is the only material suitable for fabricating electronic circuits that contain multiple layers of superconductors and other thin-film components. Operation at 77 K means that liquid nitrogen can be used as a coolant. For MRI applications, radiofrequency receivers that are currently made of copper coils can be replaced by superconducting receiver coils, increasing signal-to-noise ratio by a factor of two in some cases. This change is especially important in low-strength MRI fields (based on lower cost magnets), where weak fields mean weak signals. Superconducting coils could boost the performance of these machines by improving image quality and reducing measurement time.

Magnetic field sensing. Compared with the rest of the body's low current operations, the heart is a highly electric organ. Its faint magnetic field (about 100 picoteslas) can be measured with superconducting quantum interference devices (SQUIDs), the most sensitive magnetic sensors known. When arranged in arrays, SQUIDs can provide an image of the heart's magnetic field and yield clues to abnormal conduction patterns that are the basis of some heart arrhythmias (abnormal rhythms). About 3 million persons are treated for arrhythmias each year in the United States.

Magnetic resonance spectroscopy. Magnetic resonance spectroscopy (MRS) is similar to MRI, but instead of being tuned to the relaxation signatures of a proton, the spectrometer is tuned to a significant tissue element, such as an isotope of phosphorus in cellular adenosine triphosphate (ATP). ATP is an indicator of energy consumption in a cell, and some studies suggest that tracking its usage in cells is valuable in judging tumor response to chemotherapy. Similarly, by tuning to an isotope of oxygen or carbon, other compounds can be "viewed." Many animal studies are ongoing in this area. Receivers for this technology must be even more sensitive than for conventional MRI, because the "noise" level in these tissue studies is considerable. HTS receivers would be helpful in increasing the utility of MRS.

Medical educators may be interested in Conductus' Mr. SQUID™, an HTS product.

Potential Use to Medicine

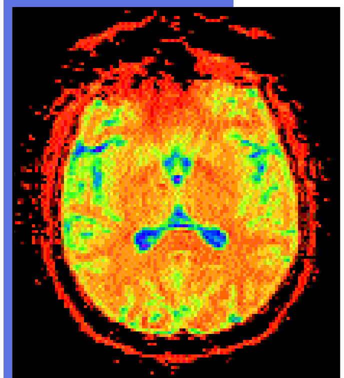
A simple component change in an MRI machine, involving the replacement of a receiver coil, can greatly improve a valuable imaging modality. Use of low-field machines can continue without the current drawback of slow, weak signal acquisition and inferior image quality. Furthermore, Conductus' development of a noninvasive device for assessment of cardiac conduction patterns will bring yet another benign diagnostic tool to medicine.

Product Status and Availability

Conductus is a leader in superconductive electronics. The company manufactures and sells both high- and low-temperature SQUIDs for nondestructive sensing and other test applications. HTS receiver coils for MRI and NMR, as well as the SQUID-based cardiac magnetic field sensor, are in the product development stage. Conductus is also codeveloping a coil with Varian for a standard NMR instrument, which will be available in late 1995.

Medical educators may be interested in Conductus' Mr. SQUID™, a sensitive superconducting magnetometer for the physics laboratory. This HTS product is the first commercial use of liquid nitrogen-cooled SQUID technology.

Real-Time Processor Speeds Up Imaging Time



Colorized MRI image of brain done on ImSyn™ breadboard. ▲

An optical processor can reduce motion artifacts and perform pattern recognition tasks.

BMDO Technology Background

Essex Corporation (Columbia, MD) is marketing a high-speed processor that could significantly cut data processing time in MRI, ultrasound, and other diagnostic examinations. It can be a freestanding or an extremely powerful add-on computer that assists the workstation by forming precise images in fractions of a second. The ImSyn™ processor is designed to handle various types of imaging, even those not uniformly sampled on a rectangular grid, such as MRI. The optoelectronic processor gives real-time processing speed to polar, spiral, or any arbitrary sampling sensor. The equipment is small and lightweight, runs on low power, and is not difficult to use.

How It Works

The processor takes data directly from any sensor, such as an MRI coil, and sends real-time imaging to the workstation for display. Standard workstation software performs image enhancement and manipulation, if desired. The system is a two-dimensional real-time Fourier transform processor with high-speed input/output that uses optoelectronic technology for speed and flexibility. Data received from the sensor are formed into images in the processor, and these images are then sent to the image analysis workstation. The pattern recognition option results by forming the complex correlation with an appropriate pattern in a database. Both processes require a minimum of support software on the host workstation.

Potential Use to Medicine

The ImSyn™ processor allows physicians to see a target tumor or other anatomical feature precisely in real time, while its high speed reduces motion artifacts that can blur images. The processor can also perform complex correlations, used in pattern recognition, with high precision. In terms of better imaging speed and the potential for computer-aided diagnosis, the processor fits in well with the projected future of medical imaging.

Product Status and Availability

The system interfaces with standard, low-end workstations such as Sun Sparc, DEC, Hewlett Packard, and Silicon Graphics. Adding the Essex processor has the potential to improve patient throughput by drastically reducing the time currently spent downloading software and preparing to receive image information from the sensor. Essex is offering preproduction units to developers; breadboard versions have been functioning since 1991.

3-D Computer Manages Complex Imagery

BMDO Technology Background

To develop technology that will allow almost instant target recognition, BMDO funded computer projects that would yield very high speed computers small enough to put on board a spacecraft. In response, Hughes Research Laboratories (Malibu, CA) is developing a very powerful small computer with potential applications that include image processing and two-dimensional signal processing. Hughes satisfied the BMDO requirement for weight and space by stacking 15 128 x 128-element, monolithic wafers in a fine-grained (complex) architecture. The design accommodates the massive data throughput generated by such procedures as MRI.

How It Works

The horizontal, two-dimensional array of processors work in lockstep while executing a common program. Functional subunits of each processor are distributed vertically. Signals travel locally within each wafer of the stack through conventional aluminum and polysilicon conductive layers. Signals are passed vertically through the stack by way of bus lines composed of feedthroughs (signal channels through the wafers) and microridges (signal channels between the wafers). All processors forming the cellular array are identical since they are composed of the same number and type of functional subunits. Computers can be assembled with computational capabilities tailored to specific applications, but the family of computers shares common architecture, instruction set, and input/output structure.

Potential Use to Medicine

Fast image processing depends on fast computing times and powerful software. Hughes' computer can address these needs in relation to diagnostic imaging. Like those destined for aircraft, medical computers that generate images from MRI, PET, and other imaging diagnostic procedures must be very robust in terms of processing ability, very fast, small, and inexpensive.

Product Status and Availability

The three-dimensional computer boasts modular construction for flexibility, fault tolerance, small size, low power consumption, and low manufacturing cost. Hughes is seeking technology partners or licensing opportunities for this promising technology.

Credit: National Cancer Institute; Bethesda, MD

▲ 3-D computing can improve resolution for many types of imaging.

Hughes is seeking technology partners or licensing opportunities for this promising technology.

Ultrasound

Now a standard imaging technique for prenatal imaging, ultrasound (US) uses ultrahigh frequency sound waves (over 20 kHz, but more often well into the MHz range) to bounce signals off anatomical features.

Strengths

Fetal imaging and echocardiography (imaging the heart) are well-established US techniques. Examination of the liver, bladder, kidney, aortic features, and even the eye, can also be accomplished with US. Advances in software and processing times have made possible three-dimensional reconstruction of US images,and research is being conducted in the assessment of fetal craniofacial abnormalities,diagnosis and presurgical staging of prostate cancer, differential diagnosis of mammogram-detected breast abnormalities, and guidance for tissue sampling. Doppler-flow US, incorporating velocity measurements of liquid flow, has proven efficacious for detection of deep-vein thrombosis (clotting) and peripheral vascular disease. US is gaining acceptance as an image guidance technique for both prostate and breast biopsy.

Limitations

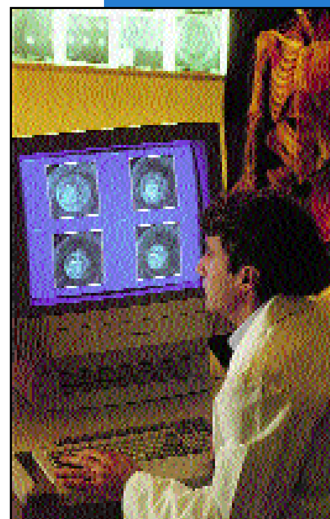
Some US imaging must be conducted though a “water window,” often requiring patients to retain a full bladder for long periods. This requirement can be quite uncomfortable, especially for pregnant women and for men with prostate disease. Some US breast imaging methods once required viewing the breast on a water-filled bag, entailing in some cases awkward anatomical placements. Innovations in this area have eliminated some of these drawbacks. Like MRI, US is currently seen as inadequate for prostate cancer screening. US is therefore used along with other diagnostic methods such as prostate-specific antigen (for prostate cancer), human chorionic gonadotrophic hormone levels (for determination of gestational age in pregnancy), and other imaging modalities. Improvements in signal extraction and amplification, as well as integration with volume-filling computer models, can help expand US’s clinical role.

Noninvasive and Novel Method for Visualization

BMDO Technology Background

ThermoTrex Corporation (San Diego, CA) has performed extensive research for BMDO in the area of advanced imaging and digital technologies. Some of this work eventually translated to a breakthrough digital mammography prototype system, which will be sold through LORAD, a division of ThermoTrex. ThermoTrex itself has also made some significant strides in ultrasonic imaging techniques including Sonic CT (computed tomography) which is suitable for breast imaging. Sonic CT holds promise for examining breast abnormalities that are not readily apparent with X-ray mammography. This technology also does not require compression of the breast, which can be painful.

Doppler CT, a variant of Sonic CT, has the potential to image blood vessels in three dimensions, assess velocities of blood flow, and assess patients with known or suspected vascular disease. For example, blocked flow in the arteries of the legs, or in the carotid arteries, which supply the brain, can be examined with this method.



▲ Sonic CT is an innovative direction in breast imaging.

How It Works

In both Sonic and Doppler CT, ultrasound signals are converted into digital images of anatomical features and can be electronically processed and stored, just as X-ray images are manipulated in what is now "conventional" CT. Sonic CT uses low-frequency ultrasound to produce cross-sectional slices of the breast, acquiring images in near-real time.

Doppler CT can measure the velocity of blood coursing through vessels. Blood flows more quickly through a passage narrowed by plaque or scar tissue than through an unobstructed blood vessel with a wider diameter. So, by comparing the speed of blood flow in adjoining areas of an artery, it can be determined whether a blockage exists in that artery. While current Doppler methods offer speedy and safe imaging, they do not offer the resolution of angiographic techniques. Doppler CT can greatly improve image resolution, although perhaps not to the fine level of contrast methods.

Potential Use to Medicine

Ultrasound requires no ionizing radiation, so its use needn't be curtailed by exposure worries. Sonic CT has the potential to spot breast abnormalities that are not associated with microcalcifications. It would be valuable in assessing such conditions as fibrocystic breast disease ("lumpy" breast disease, most often benign) and could help reduce the number of breast biopsies, 80 percent of which are negative.

Ultrasound can provide breast images that are not attainable with X-rays.

Doppler CT represents a step forward in the state of the art in Doppler imaging, and can be useful in monitoring postoperative patients who are at risk for blood clot formation. It can also be used for better measurement of carotid artery diameters (a significant concern in the aging population) and in evaluating patients with peripheral vascular disease, or "hardening" of the blood vessels in the extremities.

Product Status and Availability

Sonic CT is undergoing limited trials at the Hillcrest Center for Women's Health near San Diego. The clinical effort is being overseen by Dr. Linda Olson, a professor at the University of California at San Diego.

Doppler CT remains in the research and development phase.

Fiber Optics and Lasers

Endoscopy and laparoscopy caused a minor revolution in patient care, turning many inpatients into outpatients and reducing morbidity associated with more invasive procedures.Fiber-optic techniques have enabled remarkable strides in the visualization of internal anatomy. The nasal sinuses, esophagus,lung,colon, and bladder can all be examined and biopsied endoscopically, with far fewer complications than with exploratory surgery. Laparoscopy, a more invasive version of endoscopy, has facilitated diagnosis and treatment of gynecological disorders, liver dysfunction, and abdominal disorders.

Strengths

In addition to providing a window into the body's functions, fiber-optic technology has also provided the means to deliver laser light to tissues inside and on the surface of the body. Lasers are being used to treat dermatologic conditions such as spider veins and portwine stain birthmarks. Some ophthalmic applications include repair of retinal tears and damage caused by diabetic retinopathy. Fiber-optical endoscopy has replaced the fluoroscope for some examinations, and can be used to deliver laser light to the bladder, lungs,uterus, and gastrointestinal tract. Clinical research is under way for laser destruction of blood clots in coronary arteries, with possible future applications in smaller cerebral arteries.

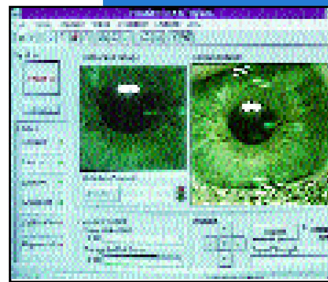
Limitations

In treatment of living tissue, laser light wavelength is selected such that only certain tissues, or components of tissues, absorb the wavelength's energy. Hemoglobin, for example, absorbs strongly in the complementary visible wavelengths of about 480 to 570 nm, which is roughly yellow-green.This wavelength has already proven to be useful for destroying intra-arterial blood clots while sparing the relatively hemoglobin-free arterial wall. In other tissues, however, it is difficult to choose a wavelength that distinguishes between benign and malignant cells, since these cells have generally similar elemental features but their structures may be quite different. Determining empirical values of cell features requires databases that contain extensive cellular information; this problem is being addressed by researchers in many fields. Low-power laser light in the ultraviolet range has the potential for examining DNA, and therefore tissue ploidy (an indicator that can help identify malignancies), but these methods must also be supplemented by specific knowledge of cancer's molecular biology. For in vivo use, the known biological effects of ultraviolet (UV) radiation must also be taken into account. This concern also exists in the use of UV lasers for corneal shaping, where corneal clouding (disturbingly similar to cataract formation) has been noted as a sequela.Shortwave UV radiation is also associated with skin cancers.

LADAR Locks Onto Eye Movements

BMDO Technology Background

Autonomous Technologies (Orlando, FL) originally developed monopulse laser radar tracking techniques for military purposes. The company received three BMDO SBIR contracts to develop laser radar (LADAR) systems for missile tracking and space docking. Today, the company has extended that technology to photorefractive keratectomy (PRK), a procedure that can improve near-sightedness by modifying the shape of the cornea.



▲ T-PRK® helps make laser surgery for myopia safer and more accurate.

In 1993 Autonomous received private investor funding to develop its T-PRK® Alpha Unit. This unit was a direct result of a prototype LADAR eye tracker developed under a BMDO SBIR Phase II project.

How It Works

The surgical effectiveness of photorefractive keratectomy depends on accurate delivery of an excimer laser beam to the surface of the cornea. Tracking the continual, involuntary eye movements known as saccades improves this accuracy and reduces dependence on patient fixation of a target. Without the ability to track and compensate for this motion, the laser beam might unintentionally ablate the wrong tissue while sculpting the cornea.

Autonomous Technologies has adapted object detection and ranging technology originally developed for missile targeting and space docking systems to track irregular eye movements. This eye tracking system, or LADARVision™, is a key component of Autonomous Technologies' new medical laser product known as T-PRK®. This surgical laser device integrates a UV excimer laser to a LADAR-based tracking system. LADAR uses laser photons reflected from a specific object for tracking or imaging.

Potential Use to Medicine

T-PRK™ is a valuable tool for the ophthalmologist who specializes in refractive surgery. It reduces the risk of inaccurate ablation caused by eye movement during laser firing. Six-month post-surgical data from a trial site in Greece show good results in procedures using T-PRK®. Preliminary data indicate that no significant loss of BCVA (best corrected visual acuity) had taken place, and minimal corneal haze, a frequent side effect of PRK, was noted. Endothelial cell density, a diminution of which would indicate cellular damage, was unaffected. Uncorrected visual acuity in 68 percent of treated eyes was 20/40 or better, with 20/20 rated as "perfect" visual acuity. Taken together, these data support the efficacy of T-PRK®.

The company hopes to receive FDA approval for the device as soon as 1997 or 1998.

Product Status and Availability

In June 1994, Autonomous and CIBA Vision Ophthalmics, a producer of ophthalmic pharmaceuticals and a business unit of CIBA Vision, formed a strategic alliance to market T-PRK®. Autonomous began clinical trials for T-PRK® in two sites in Greece and plans to have units in place for U. S. trials by mid-1996. The company hopes to receive Food and Drug Administration approval for the device as soon as 1997 or 1998. Marketing for T-PRK® has begun in several other countries.

High-Powered Lasers Stay Cool

A two-dimensional diode array for pumping a Nd:YAG slab laser.

Lasers can treat birthmarks and skin lesions that were once untreatable.

BMDO Technology Background

In 1994, Beckman Laser Institute (Irvine, CA) and Lawrence Livermore National Laboratory (LLNL; Livermore, CA) embarked on a 2-year, $1.3 million cooperative research and development agreement (CRADA) to develop laser-based medical systems. Through BMDO's Medical Free Electron Laser research in micro-optical lenses and microchannel coolers, these two groups have teamed in a CRADA to develop three laser prototype systems.

How It Works

High-power laser diodes and diode-pumped microlasers have advantages over flash-lamp-pumped solid-state lasers, but laser diodes generally have greater beam divergence, limiting the degree of focus that can be achieved. LLNL has developed a cylindrical microlens for divergence correction. The microlens focuses the radiation from each diode bar, enabling the output radiation from the diode stacks to be efficiently delivered to the end of rod lasers. The laser then operates more efficiently and can achieve higher power levels than it can without the lens. A fiber-optic pulling technique, in which the material is kept cool and viscous to retain the shape of the pre-form, can be used to manufacture thousands of the microlenses quickly and affordably.

For high-power semiconductor lasers, heat extraction from the laser-active medium is also important. The silicon microchannel cooler allows laser-diode packages to efficiently shed the large heat intensities generated at the laser-diode array with only a slight rise in temperature. These coolers are microscopic water channels buried beneath the silicon surface of the package; the channels are created using standard photolithographic techniques.

Potential Use to Medicine

The CRADA between Beckman and LLNL was established to further research in three specific areas. The first is the development of a cancer treatment called photodynamic therapy. After chemical photosensitizers are given intravenously to the patient, lasers tuned to specific wavelengths illuminate the diseased area and cause the photosensitizers to give off an oxygen radical that damages tumor cells.

Another laser system, which is still in the basic research stage, will be used in fertility treatment for both humans and animals. Lasers will drill tiny holes in the surface of eggs, increasing the chances of sperm penetrating the egg casing.

A third system will improve existing techniques for removing portwine stains (purplish birthmarks) from infants and young children. The lasers heat and destroy abnormal vessels below the skin surface, removing the discoloration after several treatments. LLNL's advances will allow physicians to adjust the duration of the laser's pulse, tailoring it to the patient. Current efforts for treatment of portwine stains center on improving energy levels of the laser pulse, and shifting the wavelength of the laser from 523 to 589 nm. A chicken allantoic membrane, which is a blood-vessel-rich embryonic membrane, is the test material.

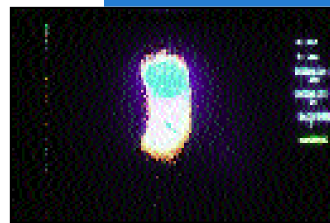
Product Status and Availability

These research methods are under development.

Optical Biopsy Promises Early Detection

BMDO Technology Background

The City College of New York's Institute for Ultrafast Spectroscopy and Lasers (IUSL) has shown that light-induced fluorescence spectroscopy can be used to distinguish normal breast tissue from cancerous breast tissue. In research derived in part from BMDO's Medical Free Electron Laser program, investigators were able to identify malignant tissue with up to 96 percent accuracy. Many other medical facilities, including those at Harvard, Yale, MIT, and the M.D. Anderson Cancer Center at the University of Texas, are pursuing studies in this area.



▲ A fluorescence image of abnormal breast tissue, using a breadboard version of the Spectral Mapping Optical Biopsy Cancer Diagnosis Unit.

How It Works

In this particular method of optical spectroscopy, the tissue under scrutiny is illuminated with a laser or a lamp light, causing the tissue to fluoresce. The characteristics of this fluorescence signature are measured to indicate chemical composition. In the studies conducted at IUSL, wavelengths from 340 to 440 nm were used to examine the collagen and elastin content of breast tissue, as well as chemical indicators of energy consumption. Consistent differences in spectroscopic signatures were seen in malignant versus benign tissue samples.

Potential Use to Medicine

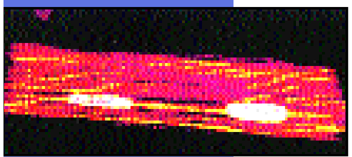
Early detection of precancerous or cancerous changes in human tissues is crucial to effective treatment of malignancies. Optical methods can help to eliminate or reduce the need for surgical biopsy and allow treatment to take place before a cancer is well-established or spreading. Optical biopsy could become an adjunct to mammography for breast cancer screening, helping to further distinguish suspicious or inconclusive images.

Fluorescence signatures of tissues can yield important information about living cells.

Product Status and Availability

These methods are in development.

Fast Lasers Take Molecular Snapshots



A living heart muscle as imaged with a two-photon scanning laser microscope, using a Clark-MXR femtosecond laser.

Very short laser pulses can used for imagery and surgery.

BMDO Technology Background

Clark-MXR (Dexter, MI) developed compact, femtosecond laser sources under the auspices of ballistic missile defense, but found a number of biological and medical applications for this device. Very short laser pulses can help to determine, for instance, the depth of a surgical incision.

A Phase I BMDO SBIR was awarded to, and completed by, Medox Research, Inc. in 1992 before it formed a joint venture with an instrumentation firm. The joint company is working on the phase II SBIR. Michigan's State Research Fund and the Michigan Department of Commerce also funded this program.

How It Works

Clark-MXR is developing small ultrafast optical sources that are more practical for applications beyond the laboratory. The company is using laser diodes—small and relatively inexpensive lasers used in laser printers—to pump femtosecond optical sources. Clark-MXR's latest pump source is 300 times smaller and 60 times lighter than traditional ultrafast optical sources. A process called self-modelocking is used to achieve this smaller and less complex design.

Traditional femtosecond optical sources also require skilled machine operators to generate short pulses, because these sources drift out of physical alignment and stop producing short pulses when left alone. As a by-product of their research on compact femtosecond optical sources, Clark-MXR developed a computer-controlled alignment system for femtosecond lasers.

Traditional optical sources have been too large for commercial applications, but these compact femtosecond optical sources open the door to many biomedical, robotic, defense, and sensor applications.

Potential Use to Medicine

According to Clark-MXR's Phillipe Bado, a femtosecond is an interval in which time is essentially frozen. In this interval, he asserts, DNA strands do not vibrate, and even the Federal deficit refrains from increase. This "flash" picture of physical phenomena helps us to understand the many steps that make up any dynamic process. Using femtosecond optical sources with ultrafast detectors, objects can be imaged directly through highly scattering media such as tissues of the human body. Instead of high energy lightwaves, which can warm the sample and cause photodamage, the femtosecond laser imaging system uses "peak power" to substitute for high energy wavelengths. These sources may be used, for example, to detect subcutaneous tumors or fluids in the lungs.

Lasers can also be used for surgery. The shorter pulse duration of femtosecond laser sources provides a clean cut, wound coagulation, and a simple way to assess the depth of the incision. Using femtosecond pulses and ultrafast detectors, the incision depth can be measured with a resolution of a few tenths of a micron. Incision depth can be measured in real time while the surgeon is operating.

The peak intensity of lasers can be used to measure molecular concentration and motion in cells. Macromolecular movement on and in living cells provides information on how cellular functions are carried out. For example, the diffusion of the low-density lipoprotein molecule on the cell surface helps regulate serum cholesterol, a health parameter that is routinely measured in cardiovascular assessment.

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Three-dimensional models of the specimen can be constructed by treating the specimen with a fluorophore—a substance that will fluoresce when appropriately excited—and applying laser beams through a complex process. Previously, this method had distorted images and induced photodamage (or photobleaching) along its path through the specimen, resulting in areas of washout within the image. A more refined two-photon excitation process, which requires ultrafast optical sources, produces ultraclear images with less work, and reduces cellular damage. Large laser sources would be impractical, but compact laser sources developed under the BMDO program will make two-photon confocal scanning an immediate commercial reality. At the basic research level, two-photon confocal microscopy has already shed considerable insight on molecular structures.

Product Status and Availability

Clark-MXR is collaborating with Dr. Ron Kurtz of the Kellogg Eye Center of the University of Michigan (Ann Arbor, MI) to evaluate the quality of laser incisions on biological tissues. The company is also working with Picometrix, Inc. (Ann Arbor, MI) on evaluating incision depths for surgical applications.

Lasers Safely Target Blood Clots

A laser safely eliminates a blood clot in this schematic drawing.

Laser thrombolysis may become a safe alternative or adjunct therapy for coronary artery blockage.

BMDO Technology Background

Unique expertise and resources residing at Los Alamos National Laboratory (LANL; Los Alamos, NM) allow the laboratory to support Theater Missile Defense (TMD) studies for BMDO. The technical capabilities involved include laser-matter coupling, remote laser sensing, and the experimental and computational study of the dynamic-hydrodynamic response of materials to pulsed heating and projectile impacts. These studies are facilitating the development of a clot-removal technique called laser thrombolysis through the work of Dr. Kenton Gregory at Providence St. Vincent's Hospital (Portland, OR). Palomar Medical Technologies (Bedford, MA) is helping to provide instrumentation.

How It Works

Laser thrombolysis, performed with standard cardiac catheterization techniques, may be a great improvement over present treatments. Using visible laser light in very short pulses, a fiber optic, coupled to the laser, is inserted into the catheter and placed 20 cm proximal to the tip of the catheter. A fluid (radio-opaque dye) is passed through the catheter and transmits the light from the end of the optical fiber through the end of the catheter to the clot, where it vaporizes the clot without damaging the arterial wall. This fluid-core optical catheter allows delivery of the laser light while washing away ambient blood. Because radio-opaque dye is used, this process can be viewed in real time via fluoroscopy.

Potential Use to Medicine

Currently, there are several ways to treat a blocked coronary artery, which can cause angina (pain) and infarction (heart attack). In balloon angioplasty, a catheter is inserted through an artery near the hip and threaded up into the major cardiac vessels. Once inserted, a balloon at the tip of the catheter is inflated, and the clot is displaced. Another treatment is enzymatic: a tissue-derived drug such as tissue plasminogen activator, (tPA), or a bacterial product called streptokinase is used to dissolve the clot. A third treatment, coronary artery bypass surgery, is performed when the previous treatments fail. All treatments have potentially significant drawbacks, and blockage frequently recurs within a year.

In laser thrombolysis, researchers hypothesize that the hemoglobin of the clot absorbs the laser light much more efficiently than the arterial wall, which means that the clot can be heated and dissolved without damaging adjacent structures. The platelets in the clot are also eliminated, which reduces the chance of a new clot forming from the released debris. Avoiding damage to the arterial wall is also important to the prevention of perforations (holes), dissection (splitting), or restenosis (renarrowing) of the artery. Since the radio-opaque dye used in these procedures is also transparent to the laser beam's wavelength, the laser method is compatible with existing catheterization protocols.

Product Status and Availability

Once developed, laser thrombolysis has the potential to treat over 100,000 patients per year. The method must undergo further refinement, and get Food and Drug Administration (FDA) approval for widespread clinical use before it can become commercially viable; however Palomar Medical Technologies is a subsidiary of a major venture capital corporation and would be suited to carry out commercialization. At present, FDA-sponsored testing involves 60 heart attack patients, over a period of 1 year, in four U.S. centers; Providence St. Vincent's Hospital (Portland, OR),

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Washington Hospital Center (Washington, D.C.), Scripps Clinic (La Jolla, CA), and Methodist Hospital (Lubbock, TX). A recent trial used a laser wavelength of 585 nm for optimal hemoglobin absorption, and light was delivered by a “flowing liquid core” catheter that allows transmission of the beam to the clot while washing away ambient blood.

A CRADA funded by the Department of Energy was initiated in early 1995 and is expected to run for 3 years. Studies involving in vitro gels that simulate clots and surgery in pigs are being conducted to define the parameters of the method and to improve safety and efficacy. LANL is lending its expertise in laser technology, computational analysis, and hydrodynamic behavior. Palomar Medical Technologies is providing lasers and catheters, and clinical and laboratory work are being conducted at the Oregon Medical Laser Center.

Gas Analysis Aids Anesthetists

Ohmeda's Rascal II anesthetic gas analyzer makes surgery safer.

BMDO Technology Background

Supported in part by BMDO's Medical Free Electron Laser program, a group of researchers from the University of Utah built a prototype Raman gas analyzer for medical gas applications. Their company was subsequently bought by Ohmeda (Louisville, CO). One of their more notable products is the Rascal II anesthetic monitor, 1,500 of which are now in U.S. operating rooms. The device is a Raman spectroscopic gas analyzer, and it enables the anesthetist to monitor physiologic gases such as oxygen and carbon dioxide, as well as anesthetic gases, in real time. The Rascal II won an R & D 100 award in 1993.

How It Works

Based on a helium-neon laser, the Rascal II directs its beam into a sampling chamber and excites the molecules of the sampled gas, sending its electrons into a higher energy level. When the electrons fall back to a lower energy level, they emit scattered light at a longer wavelength than that of the original beam. The change in wavelength is unique to the chemical composition of the gas, and this change can be measured to identify the compound.

Potential Use to Medicine

The Rascal II's ability to monitor gases in real time is of inestimable value to the anesthetist, who can observe changes in the patient's reaction to anesthesia, such as respiratory distress, and respond accordingly. Complications can develop quickly with the use of general anesthesia, so early detection of problems is very important.

Anesthetic gas analyzers are now an integral part of the operating room.

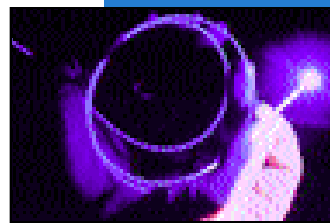
Product Status and Availability

The Rascal II is an established device, widely distributed in the United States. Ohmeda is currently designing the next generation of monitors, which will have capabilities beyond those of the current model.

Photodynamic Therapy Shows Selective Action

BMDO Technology Background

As a result of work performed at the Baylor Research Institute (Dallas, TX), partially funded by BMDO's Medical Free Electron Laser program, a number of photochemicals were studied, one of which was licensed to QLT Phototherapeutics, Inc. (Vancouver, British Columbia). This company has gone on to make excellent progress, resulting in some Food and Drug Administration-approved treatments for specific cancers, as well as significant clinical and preclinical trials for both benign and malignant conditions.



Credit: Wellman Laboratories

▲ A flexible fiber-optic coil.

How It Works

Photosensitive chemicals used in photodynamic therapy (PDT) are generally ring-structured, dye-related compounds that react with light to produce free radicals such as singlet oxygen. Well-known to students of the immune system, singlet oxygen is naturally generated by enzymes to mediate the inflammatory response to disease. This radical causes local cell damage, thereby destroying infectious agents and diseased cells. PDT reproduces this phenomenon with exogenous compounds. In QLT's protocols, the photochemicals are injected intravenously, and the affected organ is exposed to low-power laser light of a wavelength specific to the chosen photochemical. Patients thus treated must avoid exposure to the sun for 4 to 6 weeks.

Potential Use to Medicine

In treating disease, chemical agents often lack specificity. A compound as simple as aspirin, while an effective pain reliever, can also cause hemorrhage, and even ringing in the ears. Experience with photosensitive chemicals has empirically shown that diseased tissue takes up these chemicals more readily than healthy tissue. Moreover, the cell-killing activity is largely confined to the diseased tissue. This result is a great improvement over current chemotherapeutic agents, which are essentially cell poisons that don't discriminate between normal and abnormal tissues.

PDT is becoming an increasingly acceptable procedure for treating some malignancies.

Product Status and Availability

QLT is making rapid progress in testing PDT. QLT recently received FDA preapproval for Photofrin. Its generic names are dihematoporphyrin ether or sterile porfimer sodium. Photofrin has been approved in Canada for bladder cancer treatment and in Canada, the Netherlands, and Japan for lung and esophageal cancer.

QLT is testing a second-generation benzoporphyrin derivative (BPD) in phase II clinical trials on psoriasis and basal cell carcinoma in the United States and Canada. In conjunction with CIBA-Geigy, QLT is also conducting a phase I clinical trial of BPD for macular degeneration, a common age-related eye disease, in the United States and Europe. BPD is also seen as a possible treatment for breast cancer recurrences on surgical incisions. Preclinical work is being conducted with BPD for preventing restenosis after balloon angioplasty and, based on BPD's observed effects on T-cell activation, for rheumatoid arthritis.

CIBA-Geigy has licensed zinc pthalocyanine to QLT. Tests with this compound, which are in the preclinical stage, suggest that it is a candidate for topical treatments in dermatology, for conditions such as psoriasis, or malignancies such as basal cell carcinoma.

PET, SPECT, and Particle Beam Therapies

Positron emission tomography (PET) is a minimally invasive imaging procedure that uses radioactively tagged metabolites to image organs and to illustrate some metabolic pathways.Blood flow in the brain, for instance, can be viewed by injecting fluorine-tagged glucose into the blood-stream. The radioactive fluorine emits positrons, which collide with electrons, to produce two gamma rays that travel in opposite directions. The gamma rays strike a scintillator, and an image of the organ is formed.

Strengths

As the brain uses about 60 percent of the blood's glucose content, the tagged compound quickly accumulates in cerebral tissues. By issuing cognitive tasks to the subject under scrutiny, one can see which parts of the brain are active during reading, counting,speaking, and so on. A fast-growing tumor, with its avid appetite for glucose, can also be imaged. Areas affected by occlusive stroke can be identified by their failure to take up the isotope.

SPECT, or single photon emission computed tomography, is a cousin of PET. It also uses radiopharmaceuticals, but it uses tomographic techniques to image their distribution. Thus, as in computerized axial tomography scanning, slices of the anatomy can be viewed, eliminating interference from overlying tissues.

Particle accelerators are used to produce isotopes of carbon, oxygen, nitrogen, and fluorine for PET and SPECT. Accelerators can also be used in directed energy therapies, such as proton delivery to deep-seated tumors. This type of energy delivery has advantages over conventional radiation therapy. The beam of ions can be controlled and focused by magnetic fields, delivering maximum destruction to the tumor and helping to spare normal cells. By contrast, X-ray therapy suffers from scatter and attenuation as radiation travels through healthy tissue, and can cause undesirable and sometimes grave side effects.

Limitations

Both PET and SPECT expose the individual to limited amounts of ionizing radiation.

Affordable Particle Beam Therapies

BMDO Technology Background

AccSys Technology, Inc. (Pleasanton, CA) developed a superconducting radiofrequency quadrupole linear accelerator (RFQ linac) in cooperation with Argonne National Laboratory (ANL), using funding from BMDO and the Department of Energy. Developed to improve BMDO's neutral particle beam systems, the compact RFQ linac can replace large, prohibitively expensive cyclotrons for use in radioisotope production.

▲ Conceptual drawing of AccSys' Pulsar™ apparatus.

How It Works

Using powerful electromagnetic fields, an RFQ linac hastens charged particles along a pathway until they reach a speed that is useful in such high-energy tasks as bombarding elements to produce unstable isotopes or delivering high-speed protons to a deep-seated tumor. AccSys and ANL participated in a cooperative research and development agreement (CRADA) to employ superconducting materials in a prototype device, cooled to 4.6 K with liquid helium. Positively or negatively charged hydrogen molecules can be accelerated and delivered to cancer cells. Radioisotopes such as oxygen-15 and fluorine-18 can also be produced.

Potential Use to Medicine

Accelerated ions such as protons can be delivered to biological tissues with less collateral damage than that associated with X-ray exposure. Superior beam delivery is another advantage of particle accelerators, with minimal attenuation of the directed energy. Radioisotopes for such tracer pharmaceuticals as fluorinated glucose (fluorine-18 coupled to glucose), which in turn can be used to illustrate metabolic processes in PET, can also be manufactured with RFQ linacs.

High-energy beams can target tumors with little collateral damage.

Product Status and Availability

An AccSys room-temperature proton linac, also based on BMDO-funded development, was installed at Loma Linda University Proton Cancer Treatment Center (Loma Linda, CA) in 1990. Loma Linda is treating 50 to 60 cancer patients a day with the directed energy therapy. Up to four patients can be treated simultaneously in the center's $80 million facility.

AccSys' Pulsar™ room-temperature product series offers state-of-the-art design, compactness, multiple-beam configurations for simultaneous delivery to multiple targets, and an upgradeable system. The system is affordable and self-shielding, and lends itself to widespread use in clinical settings. It can deliver both protons and negatively charged hydrogen ions.

The Pulsar™ can also be used to produce oxygen-15 (water, diatomic oxygen, and carbon monoxide), nitrogen-13 (in the form of ammonia), carbon-11 (carbon dioxide or monoxide), and fluorine-18 (fluorine ion or fluorine-tagged glucose). AccSys is working under a joint agreement with the PET chemistry group at Brookhaven National Laboratory to further develop appropriate targets for the Pulsar™.

Sensitive Photodiodes Reduce Cost, Increase Resolution

API's photodiode technologies can improve the resolution and sensitivity of medical images.

BMDO Technology Background

Advanced Photonix, Inc. (API; Camarillo, CA) has developed large-area silicon avalanche photodiodes that are among the first solid-state devices to provide a high-gain, low-noise, large-area replacement for photomultiplier tubes (PMTs) used in a selected range of light detection applications. Avalanche photodiodes bring the same qualities of ruggedness, small size, and low cost to light detection and imaging that other semiconductors have brought to the rest of the world of electronics.

Early research on API's avalanche photodiodes, supported in part by a 1987 BMDO SBIR contract, was conducted at Xsirius Scientific, Inc. (Los Angeles, CA). In 1988, Xsirius formed API to commercialize this technology. In 1992, API received another BMDO SBIR contract to develop single-chip photodetector arrays; these arrays are made by subdividing large-area avalanche photodiodes into an array of isolated pixels.

How It Works

API's photodiode arrays fill the gap between large-format focal plane arrays, which have the pixels to resolve images spatially but lack the sensitivity needed for many applications, and PMTs, which are very sensitive but lack the pixels needed for spatial resolution. API's arrays also make detectors more sensitive over longer distances, permit fabrication of multichannel receivers with a larger field of view, and give detectors a higher dynamic range.

API's avalanche photodiodes can detect light in all visible wavelengths and in parts of the ultraviolet and infrared spectra. They can also directly detect X-rays and charged particles, and can detect gamma rays when they are coupled to scintillating crystals or fibers.

Avalanche photodiodes can directly detect X-rays and provide larger fields of view for medical imaging.

Potential Use to Medicine

The capabilities of API's photodiode arrays will be important in medical imaging applications where sensitivity and resolution (both energy and time) are important. Photodiode arrays can indirectly sense gamma emission in PET, gamma camera, and SPECT applications. API is currently pursuing PET imaging applications in a contract with CTI PET Systems, Inc. (Knoxville, TN).

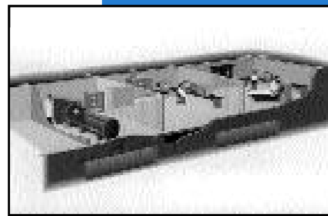
Product Status and Availability

In the CTI contract, API is building photodiode arrays for CTI to incorporate into its PET scanners. While API has already built some prototype arrays for this contract, the company is working to improve the detectors' reliability through enhancements in wafer processing. API would like to increase the current avalanche photodiodes' reliable lifetimes of about 1 year to at least 5 years. If successful, CTI PET Systems will have the first option to license the technology for this application.

Smaller, Lighter Accelerators Boost PET Availability

BMDO Technology Background

With the help of a proof-of-principle contract for the BMDO SBIR program (plus follow-on funding from the Department of Energy and the U.S. Army Research Laboratory), North Star Research Corporation (Albuquerque, NM) has developed a compact, direct current accelerator that employs a series of nested stages, each one totally isolated from the others, to accelerate particle beams of protons, electrons, neutrons, and heavy ions. Because it employs nested stages, this accelerator, known as the Nested High Voltage Generator (NHVG™), is smaller, lighter, more reliable, and less expensive than traditional direct current accelerators.



▲ PracSys implements North Star's accelerator technology in a complete PET system.

How It Works

Nested stages are based on the principle of the Faraday cage, which allows the construction of a series of concentric shells one inside the other, each one electrically isolated from the others. In the NHVG™, electronics internal to each shell maintain a preset voltage difference from one stage to the next.

The electrical isolation provided by this scheme greatly reduces the accelerator's size, weight, and cost. In addition, the nested stages are designed so that an electrical breakdown in one stage does not stress the others. Therefore, if a few stages fail, the accelerator can continue operation with no risk of further damage to the machine. Failed stages can then be replaced in a single day, greatly reducing the accelerator's maintenance downtime.

The NHVG™ can operate both in a tandem mode and a single-ended electrostatic mode. Tandem-mode operation provides higher kinetic energy levels with less power output; however, it can only accelerate certain particles, such as the proton or deuteron. Single-ended accelerators, though less efficient, can accelerate any particle.

Compact accelerators are replacing cyclotrons for the generation of radiopharmaceuticals.

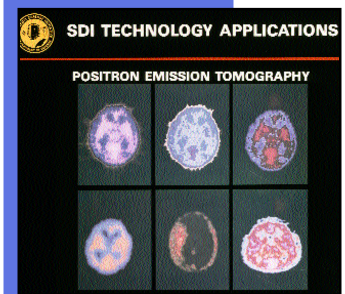
Potential Use to Medicine

A tandem-mode NHVG™ can replace larger, more expensive cyclotrons used to produce radiopharmaceuticals needed for PET imaging. Direct-beam radiotherapy is another possible medical application.

Product Status and Availability

Accelerators for medical use are licensed to PracSys Corporation (Woburn, MA) for distribution.

Tandem Cascade Accelerator Finds Multiple Applications



PET images show chemical activity in the brain.

SRL's accelerators are compact and cost-effective.

BMDO Technology Background

Science Research Laboratory (SRL; Somerville, MA) has developed compact electrostatic accelerator technology that uses three advanced components developed under BMDO SBIR contracts: an all-solid-state high-voltage power supply, a high-current negative ion source, and a user-friendly automated control system. These innovations allow SRL's cascade accelerators to provide ion beam currents up to 10 times higher than conventional cyclotrons at one-half the size, one-fifth the weight, and one-half the cost.

How It Works

Electrostatic accelerators use strong electric fields to accelerate charged particles through an evacuated tube; the stronger the voltage difference between the ends of the tube, the greater the final acceleration. However, rather than producing one large voltage drop at each end of the accelerator, these accelerators have a cascading series of electrodes that distribute the electric field more evenly throughout the accelerator and permit more control over the beam. SRL's cascade accelerators can produce beams of protons, deuterons, and electrons with an energy of up to 6 MeV.

SRL currently operates three engineering prototypes of the cascade accelerator: a 600 keV deuteron accelerator, a 600 keV electron accelerator, and a 3.7 MeV proton and deuteron tandem cascade accelerator (TCA). The TCA achieves higher energies through a design in which a negatively charged hydrogen ion is stripped of its electrons halfway through the accelerator (making it a positively charged proton). Because the positive ions will accelerate to double the speed with an easily reversed voltage difference, this scheme transmits maximum kinetic energy with minimum power output.

Potential Use to Medicine

The TCA was designed to produce radioisotopes for PET. To be used for this application, accelerators must produce the four most common radioisotopes—fluorine-18, nitrogen-13, oxygen-15, and carbon-11. With the help of the BMDO miniaturized PET accelerator program, SRL has developed the targetry and the robotic radioisotope synthesis system needed to adapt the TCA to the task of radiopharmaceutical production.

Other medical applications for SRL's accelerator technology include boron neutron capture therapy for treating deep-seated brain tumors; dual-energy, digital subtraction angioplasty for noninvasive imaging of the coronary arteries; and gamma resonance imaging for nutritional assessment. Gamma resonance imaging can image certain elements, such as nitrogen or calcium, that selectively absorb radiation produced when an ion beam is directed onto a target material.

Product Status and Availability

In May 1993 the TCA-based radioisotope delivery system was installed in the new Neuroimaging Research Center at the Washington University School of Medicine (St. Louis, MO), one of the foremost PET imaging centers in the world. Since then, the TCA has routinely generated three different oxygen-15 radiopharmaceuticals for the center, and demonstrated the ability to produce fluorine-18 and nitrogen-13. Reliability of the TCA system has been excellent, producing as many as 20 batches of radiopharmaceuticals in a day (limited only by operators' time, not the machine) and operating with virtually no maintenance downtime.

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The TCA is now on schedule to become the major source of radiopharmaceuticals for the Neuro-PET program at Washington University. A scanner will be installed directly above the TCA and delivery lines of the oxygen-15 system have been installed from the TCA to the PET room. In addition, human-use approval is currently being sought for TCA radiopharmaceuticals.

SRL also has had discussions with more than 15 organizations interested in commercializing PET imaging systems and is now receiving inquiries from potential customers for the TCA-based PET systems.

Linear Accelerators Replace Cyclotrons

BMDO Technology Background

Science Applications International Corporation (SAIC; San Diego, CA) is developing a PET Tracer Production System that will replace cyclotron accelerators, which weigh a minimum of 20 tons. SAIC's system, which is about 17 feet long and weighs about 2 tons, consists of three RFQ linacs, the targets in which the radioisotope materials are created, and the chemical processing systems that synthesize the final radiopharmaceuticals required for PET. SAIC is developing the RFQ linac and the University of Washington Medical Center, a subcontractor, is developing the targets and chemical processing systems.

SAIC began developing this system with funding from BMDO's Miniaturized PET Accelerator Program, which aimed to transfer new accelerator developments resulting from BMDO programs to the medical arena. SAIC was awarded this competitive contract because its approach had a high content of ballistic missile defense technology and offered many advantageous innovations. SAIC has continued development of the accelerator on its own since the program terminated in 1992.

An inside view of an RFQ linac from SAIC. ▲

How It Works

The heart of this PET radioisotope production system is the RFQ linac, which uses powerful electromagnetic fields to accelerate and bunch charged particles. Particles are accelerated into a target material and the high energy of this collision initiates a nuclear reaction that produces the radioisotopes needed for PET imaging.

RFQ linacs can help to make PET systems more affordable.

Potential Use to Medicine

PET allows doctors to visualize metabolic processes in organs such as the brain and heart. Linacs have largely replaced cyclotrons in the production of radioisotopes used for PET. As a result, cost and space requirements have come down, allowing on-site facilities to be installed at hospitals and clinics.

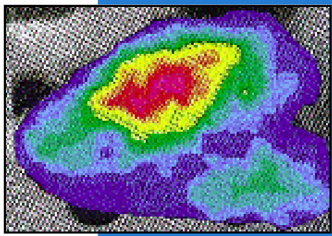
Product Status and Availability

In 1994, SAIC formed a development partnership with the Fermi National Accelerator Laboratory (Batavia, IL), the Biomedical Research Foundation (Shreveport, LA), and the University of Washington. Under this partnership, which is being funded by the Department of Energy, SAIC will test its PET Tracer Production System at the Biomedical Research Foundation, one of the best clinical PET facilities in the world.

Highly Efficient Scintillating Fibers

BMDO Technology Background

Researchers at the University of Texas at Dallas (Richardson, TX) are using plastic scintillating fibers and position-sensitive photomultipliers to increase the efficiency of gamma ray detectors used in PET and SPECT imaging. The scintillators developed at UT-Dallas are made of polystyrene fibers that increase detector resolution and efficiency, resulting in detectors with excellent spatial (less than 1 mm) and time (less than 10 nanoseconds) resolution. UT-Dallas and the University of California at Los Angeles originally developed the scintillation fiber and position-sensitive photomultiplier technique as part of a BMDO project to build a space-based gamma ray telescope.



▲ PET image of an animal brain, using copper-64.

How It Works

This system works by converting incident gamma rays into visible light. When the gamma ray photons hit the scintillating fibers, the fibers emit electrons through Compton scattering or the photoelectric effect. As these electrons pass through the scintillating fiber, atoms are excited to a higher energy state. When the atoms return to the ground state, they emit light that is detected by position-sensitive photomultipliers. The signal from these photomultipliers can then produce a digital image of the original gamma ray emission.

UT-Dallas technology can sharpen PET and SPECT images.

Potential Use to Medicine

UT-Dallas is now working with the University of Texas Southwestern Medical Center at Dallas to apply its gamma ray detector to SPECT and PET imaging. In both processes, a radioactive isotope is administered to a patient so that the isotope accumulates in the organ to be imaged. The isotope emits gamma radiation or, in the case of PET, positrons that produce gamma rays. The scintillators developed at UT-Dallas can increase the spatial resolution of SPECT and PET imaging about tenfold, depending on the fiber size. This increase results in sharper PET and SPECT images. Improved time resolution also will minimize background noise and accidental readings. The group also plans to use the detector technique in miniaturized endoscopic probes or imagers.

Product Status and Availability

The University of Texas system, along with some venture capital investors, has formed a spinoff company named Epikon, Inc. to further develop and commercialize this technology. A commercial prototype SPECT/PET camera based on this technology should be ready in less than 2 years. In the meantime, research continues to improve on the scintillating detector concepts and photosensor devices.